REMARKS

A. Status of the Claims

Prior to the filing of this paper, claims 11-13 were presented for examination and claims 1-10 and 14-15 were withdrawn from consideration as being directed to a non-elected invention. In this paper, Applicants have cancelled claims 1-10 and 14-15 without prejudice or disclaimer. In addition, Applicants have added new claims 16-32. When these claim amendments and deletions have been entered, the claims presented for examination will be claims 11-13 and 16-32.

The Examiner has maintained rejections of Claims 11-13 under 35 U.S.C. §102(b) for allegedly being anticipated over the following four references:

(a) Wessels et al., Infection and Immunity, vol. 66, no. 5, pp. 2186-2192, May 1998, ("Wessels I").

(b) Wessels et al., Journal of Clinical Investigation, vol. 86, pp. 1428-1433, November 1990, ("Wessels II").

(c) Michon et al., In Streptococci and Host. (Ed). Horaud et al., Plenum Press, New York, pp. 847-850, 1997, ("Michon I").

(d) Jennings et al., U.S. Patent No. 5,993,825, ("Jennings").

In addition, the Examiner introduced two new rejections: (i) a rejection of claims 11-13 under 35 U.S.C. §102(b) for allegedly being anticipated by U.S. Patent No. 5,785, 973 to Bixler ("Bixler"); and (ii) a rejection of claims 11-13 under 35 U.S.C. §103(a) for allegedly being unpatentable over U.S. Patent No. 6,602,508 to Michon et al. ("Michon III") in view of U.S. Patent No. 5,443,966 to Fairweather ("Fairweather").

B. Explanation of the Amendments

Applicants have amended claim 11 to specify that "the Fragment C in the conjugate vaccine is not part of a whole tetanus toxoid molecule." Support for this amendment is generally found throughout the specification. See, *e.g.*, WO2005/000346 at ¶[22]. Claim 11 now also specifies that "the conjugate vaccine does not increase a patient's anti-tetanus titer response." Support for this statement is found, for example, in Tables 3 and 4 of Applicants' specification [WO2005/000346, pages 13 and 15, respectively].

In addition, Applicants have added new claims 16-32. These claims are also supported throughout the specification (see, *e.g.*, WO2005/000346 at ¶¶[022], [27] and original claim 13.) Applicants respectfully submit that no new matter has been added by these amendments.

C. Rejections under 35 U.S.C. §102(b)

1. Applicants' Claims Are Not Anticipated by Wessels I, Wessels II, Michon I or Jennings

Applicants respectfully traverse the rejection of claims 11-13 under 35 U.S.C. § 102(b) for allegedly being anticipated by Wessels I, Wessels II, Michon I and Jennings. Briefly, the prior art references do not disclose all of the features of the claimed invention. Accordingly, the rejection should be withdrawn.

Independent claim 11, as amended, reads as follows:

> 11. A conjugated vaccine comprising an antigen that has been conjugated to Fragment C, wherein the Fragment C does not exist in the conjugate vaccine as part of a whole tetanus toxoid molecule. (emphasis added).

In the prior Office Action, the Examiner acknowledged that Wessels I, Wessels II, Michon I and Jennings do not disclose "Fragment C" in any context except as part of the full length tetanus toxin. Office Action dated March 20, 2009, at ¶¶8-11. Claim 1, as amended, specifies that the "Fragment C does not exist in the conjugate vaccine as part of a whole tetanus toxoid molecule." Wessels I, Wessels II, Michon I, and Jennings do not meet this feature of claim 11, as the Examiner conceded in the prior office action. Accordingly, each of these references fails to disclose each and every feature of the presently claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the 35 U.S.C. §102(b) rejections of claims 11-13 over Wessels I, Wessels II, Michon I and Jennings.

2. Applicants' Claims Are Not Anticipated by Bixler

Applicants respectfully traverse the rejection of claims 11-13 for allegedly being anticipated over Bixler. Bixler does not disclose the use of Fragment C in a conjugate vaccine, as specified in the presently pending claims. More particularly, while Bixler does compare the ability of the H, L, and C fragments of tetanus toxin to stimulate murine T-cell proliferation, it only does so in the context of trying to isolate a single T-cell epitope for use in its conjugates. It is for this reason that Bixler exposes Fragment C of tetanus toxin to further digestion by other enzymes, including pronase, ficin, subtilisin, and V8, and then subjects the digested fragment C of tetanus toxin to separation techniques such as HPLC. [Bixler, col. 33, lines 30-41, and col. 33 line 45 to col. 35, line 2]. Other evidence that Bixler only contemplates the use of a portion of Fragment C possessing one epitope in its conjugates is given in both the specification and the claims of Bixler. For example, Bixler states at col. 8, lines 16-20 that single epitopes are advantageous over larger peptides that contain such epitopes:

> the use of the T-cell epitope, per se, as opposed to a larger peptide containing the epitope, provides an economic advantage in that it may be readily synthesized as well as a safety advantage in avoiding the use of the whole protein" (emphasis added).

This statement, in and of itself, is a clear teaching away from using Fragment C of tetanus toxin in a conjugate vaccine, as presently claimed, since Fragment C contains more than one epitope. Additionally, claims 1, 8 and 9, which are the only independent claims of Bixler that recite "tetanus toxin" explicitly recite that only one epitope is present in the claimed conjugate:

> 1. An immunogenic conjugate consisting of a polysaccharide antigen covalently bound to **one T-cell epitope** of tetanus toxin, diphtheria toxin or pertussis.
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> 8. An immunogenic conjugate consisting of a polysaccharide antigen covalently bound to **a T-cell epitope** which is **amino acid residues 961-980** of tetanus toxin, or a variation thereof consisting of the addition of a lysine or a cysteine, with or without a glycine spacer element, to the amino terminus of the T-cell epitope, which epitope retains the ability to stimulate T-cells.
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> 9. An immunogenic conjugate consisting of a polysaccharide antigen covalently bound to **a T-cell epitope** which is **amino acid residues 1021-1040** of tetanus toxin, or a variation thereof consisting of the addition of a lysine or a cysteine, with or without a glycine spacer element, to the amino terminus of the T-cell epitope, which epitope retains the ability to stimulate T-cells.

(Bixler also makes it clear that amino acid residues 961-980 and 1021-1040 of tetanus toxin, as claimed in claims 8 and 9, are in fact two separate epitopes [Bixler, col. 34, line 67 to col. 35, line 2]).

In contrast to Bixler, Applicants' invention is directed to conjugate vaccines that use fragment C of tetanus toxin, which Bixler clearly shows to contain more than one epitope [see Bixler, cols. 33-35]. Importantly, Applicants' inventive conjugates, though containing more

than one tetanus toxin epitope, do not increase the anti-tetanus titer response of a patient injected with the conjugate. This statement is supported, for example, by Table 3 of Applicants' specification [see WO2005/000346, page 13]. The ELISA results of Table 3 show that the anti-tetanus titer for the GCMP-TTc and recombinant GCMP-TTc conjugates remains less than 0.02 IU/ml over 52 days, whereas the anti-tetanus titer for the full TT conjugate increases to 54.5 IU/ml over 52 days. This indicates that Applicants' inventive TTc-based conjugates advantageously do not raise antibodies to the full tetanus toxin. Nevertheless, the potency of Applicants' TTc-based conjugates against the polysaccharide component is essentially the same as that of conjugates involving the full tetanus toxin, as shown in Applicants' Figures 3 and 4.

Thus, one aspect of Applicants' invention is the discovery that it is not necessary to restrict the tetanus toxin fragment to just one epitope to obtain the benefits of improved safety.

Moreover, Applicants' use of a Fragment C is advantageous for another reason. When Applicants' inventive conjugate enters a patient's body and is expressed at the surface of antigen-presenting cells, more than one epitope is presented at the surface because fragment C of tetanus toxin contains more than one epitope. This leads to a higher chance of subsequent recognition by T-cells, which corresponds to a more potent immune response against the polysaccharide.

For these reasons, Applicants respectfully assert that the pending claims are not anticipated by or obvious over Bixler.

D. Rejections under 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 11-13 under 35 U.S.C. §102(e) for allegedly being unpatentable over Michon III in view of Fairweather. Briefly, the combination of references fails to teach or suggests all of the features of the claimed invention. Accordingly, the rejection should be withdrawn. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (holding that obviousness requires a suggestion of all limitations in a claim).

As amended, Applicants' claim 11 is directed to "a conjugate vaccine comprising an antigen that has been conjugated to Fragment C… wherein the conjugate vaccine does not increase a patient's anti-tetanus titer response." Nowhere are these claimed features taught or suggested in either Michon III or Fairweather. More particularly, Michon III does not even mention Fragment C (which the Examiner now concedes), much less a Fragment-C-containing conjugate vaccine that"does not increase a patient's anti-tetanus titer," as specified in the claims. Similarly, Fairweather does not teach or suggest a conjugate vaccine that "does not increase a patient's anti-tetanus titer response." In fact, if anything, Fairweather teaches that Fragment C would necessarily increase the anti-tetanus titer, because Fairweather reports that Fragment C can be used directly in vaccines for conferring immunity to tetanus. Fairweather, 3:20-25. For at least these reasons, the claimed invention is not obvious over the combination of Michon III and Fairweather. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3732, Order No. 00518-105029.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No.13564-105027.

Respectfully submitted,
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